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(54) Title: PREPARATION OF 1-BUTYL-4-PIPERIDINYLMETHYLAMINE

(57) Abstract

A process for the preparation of 1-butyl-4-piperidinylmethylamine, which process comprises: i) the reaction of isonipecotamide and 1-bromobutane to give the N-butyl derivative of isonipecotamide; followed by ii) reduction with $LiAlH_4$, characterised in that the reactions i) and ii) are carried out in toluene as solvent.

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PREPARATION OF 1-BUTYL-4-PIPERIDINYLMETHYLAMINE

This invention relates to a new synthetic process to an intermediate which is useful for the preparation of compounds having pharmacological activity.

WO 93/03725, WO 93/05038, WO 93/08187, WO 93/16072, WO 93/18027, WO 93/18036, WO 94/07859, WO 94/08965, WO 94/08994, WO 94/08995, WO 94/08998, WO 94/17071 (SmithKline Beecham plc) describe compounds having 5-HT_4 receptor antagonist activity.

WO 93/18036 , Example 3 describes N-[(1-^{n}butyl-4-piperidyl)methyl]-3,4-dihydro-2H-[1,3]oxazino[3,2-a]indole-10-carboxamide SB 207266, (the hydrochloride salt is SB 207266-A) which is being developed by SmithKline Beecham plc as the active ingredient in a medicament for treatment of irritable bowel syndrome.

WO 93/18036 describes a method of preparation of SB 207266-A from N-[(1-^{n}butyl-4-piperidyl)methyl]indole-3-carboxamide (i.e. the compound corresponding to SB 207266, without the oxazino moiety), by reacting with N-chlorosuccinimide and 3-bromo-1-propanol, followed by treatment with sodium carbonate. N-[(1-^{n}butyl-4-piperidyl)methyl]indole-3-carboxamide is prepared by coupling 1-butyl-4-piperidinylmethylamine with indole-3-carboxylic acid. The 1-butyl-4-piperidinylmethylamine is prepared as in Description 7 of WO 93/05038 and Description 1 of WO 93/18036, in a three stage process from isonipecotamide and 1-bromobutane, by alkylation in ethanol, to give the N-butyl derivative of isonipecotamide which is dehydrated to the corresponding nitrile and then reduced with $LiAlH_4$ in ether.

An alternative process for preparing 1-butyl-4-piperidinylmethylamine has now been discovered which involves the use of a common solvent, allowing the two stages to be run without isolation of the N-butyl derivative of isonipecotamide.

Accordingly, the present invention provides a process for the preparation of 1-butyl-4-piperidinylmethylamine, which process comprises:

i) the reaction of isonipecotamide and 1-bromobutane to give the N-butyl derivative of isonipecotamide; followed by

ii) reduction with $LiAlH_4$,

characterised in that the reactions i) and ii) are carried out in toluene as solvent.

The advantages of this process as compared with that previously described are as follows:

1. Toluene does not contain any additives, whereas THF contains a stabiliser (di-*t*-butylcresol) which can only be removed from 1-butyl-4-piperidinylmethylamine by fractional distillation.

2. The overall process does not involve the preparation/isolation of the intermediate nitrile, and is therefore one step shorter.

3. The process does not involve the isolation of the N-butyl derivative of isonipecotamide.

4. The process uses a single solvent and eliminates the use of ethanol, chloroform and THF.

5. the special extractive work-up of the $LiAlH_4$ reaction reduces the usage of solvent and loss of product on solid alumina residues.

The following Examples illustrate the invention.

Example 1

4-Piperidinecarboxamide (*iso*-nipecotamide) and potassium carbonate (2 equivs.) were stirred in toluene and treated with 1-bromobutane (1 equiv.). The reaction mixture was heated at reflux (107-110°C) for 2 hours. After cooling to 80-85°C the mixture was washed with hot water followed by hot aqueous potassium carbonate solution. The resulting toluene solution of 1-butyl-*iso*-nipecotamide was dried by azeotropic distillation, maintaining the reaction volume by addition of fresh toluene.

The toluene solution was cooled to 0-5°C, under nitrogen. A solution of $LiAlH_4$.2THF in toluene (1.0 molar solution; 2.0 equivs.) was added over 1 hour, keeping the temperature <10°C. The mixture was allowed to warm to room temperature and was then heated to reflux for 1 hour. After cooling to 0-5°C, 32% w/w sodium hydroxide solution (1.5 equivs. wrt substrate) was added cautiously over 1 hour, keeping the temperature <10°C. The mixture was stirred for 30 minutes at ambient temperature and the precipitate filtered through celite, washing the bed thoroughly with toluene. The filtrate was evaporated *in vacuo* to give 1-butyl-4-piperidinylmethylamine as a pale yellow oil, containing ~13% by weight toluene, in 72% yield (after adjusting for toluene content).

Example 2

Alternatively the first part of the preparation may be carried out as follows:

4-Piperidinecarboxamide (*iso*-nipecotamide) and 5M aqueous potassium carbonate solution (2 equivs.) were stirred in toluene and treated with 1-bromobutane (1 equiv.). The reaction mixture was heated at reflux (107-110°C) for 2 hours. After cooling to 70-80°C the mixture was washed with hot water followed by hot aqueous potassium carbonate solution. The resulting toluene solution of 1-butyl-*iso*-nipecotamide was dried by azeotropic distillation, maintaining the reaction volume by addition of fresh toluene.

Example 3 A 3L vessel was purged with nitrogen and charged with *iso*-nipecotamide (112.1g 0.87mol) and dry toluene (785ml). The suspension was warmed to 50°C and potassium carbonate (248g, 1.79mol) and butyl bromide (119.8g,

0.87mol) were added in one portion. The resulting mixture was heated at reflux under Dean-Stark conditions for three hours and then cooled to 65°C and quenched by addition of water (875ml). The aqueous phase was separated at about 80°C and the organic layer dried by azeotropic distillation of toluene (200ml). Fresh toluene (200ml) was added to maintain a constant volume.

The reaction mixture was cooled to about 5°C and treated, dropwise, with a solution of lithium aluminium hydride.2THF in toluene (500ml, 3.5M, 1.75mol). The mixture was stirred at ambient temperature for one hour and then at about 55°C for a further two hours. The reaction was then quenched by cautious addition of sodium hydroxide solution (1200ml, 10.8M) and heated to about 70°C. The aqueous phase was separated and washed twice with toluene (300ml each wash). The combined organic washes were concentrated under reduced pressure and the product 1-butyl-4-piperidinylmethylamine (SB-211156) (127g) was isolated as a pale yellow oil in 85% yield by vacuum distillation (bp 106°C at 20mm Hg approx.).

Claims

1. A process for the preparation of 1-butyl-4-piperidinylmethylamine, which process comprises:

i) the reaction of isonipecotamide and 1-bromobutane to give the N-butyl derivative of isonipecotamide; followed by

ii) reduction with $LiAlH_4$,

characterised in that the reactions i) and ii) are carried out in toluene as solvent.

2. A process according to Claim 1 in which the reaction mixture after the reduction is treated with hot sodium hydroxide solution and the mixture is extracted with an organic solvent.

3. A process for the preparation of SB 207266, or a pharmaceutically acceptable salt thereof, which process comprises preparing 1-butyl-4-piperidinylmethylamine according to the process of claim 1, followed by coupling with an appropriate indole 3-carboxylic acid derivative, and thereafter as necessary converting the indole and/or substituents, including cyclisation to 3,4-dihydro-2H-[1,3]oxazino[3,2-a]indole.

4. SB 207266 whenever prepared by the process of Claim 3.

INTERNATIONAL SEARCH REPORT

Inter onal Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D211/26 C07D498/04 //(C07D498/04,265:00,209:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 93 05038 A (SMITHKLINE BEECHAM PLC) 18 March 1993 cited in the application see description 7 and claims	1-4
A	WO 93 18036 A (SMITHKLINE BEECHAM PLC) 16 September 1993 cited in the application see description 1 and claims	1-4
A	WO 94 08965 A (SMITHKLINE BEECHAM PLC) 28 April 1994 cited in the application see description 1-5 and claims	1-4
P,A	WO 96 38420 A (NISSHIN FLOUR MILLING CO., LTD.) 5 December 1996 see page 55, example 38	1,2

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Information on patent family members

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